



(19)

Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 0 602 014 B2

(12)

NEW EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the opposition decision:
10.10.2001 Bulletin 2001/41

(51) Int Cl.7: **A61M 1/16, A61K 9/14**

(45) Mention of the grant of the patent:
29.12.1997 Bulletin 1997/52

(21) Application number: **94102866.4**

(22) Date of filing: **25.05.1990**

(54) Preparation for blood dialysis and method for production thereof

Zubereitung für die Hämodialyse und deren Produktionsmethode

Préparation pour la dialyse du sang et sa méthode de production

(84) Designated Contracting States:
BE DE FR GB IT NL SE

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(30) Priority: **26.05.1989 JP 13433989**
26.05.1989 JP 13434089
06.07.1989 JP 17312089

(43) Date of publication of application:
15.06.1994 Bulletin 1994/24

(62) Document number(s) of the earlier application(s) in
accordance with Art. 76 EPC:
90401405.7 / 0 399 918

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EP-A- 0 177 614	EP-B- 0 086 553
WO-A-81/03180	

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Description**Field of the Invention:**

5 [0001] The present invention relates to a preparation for blood dialysis and a method for the production thereof. More particularly, it relates to a uniform preparation for blood dialysis excellent in stability of storage and a method for the production thereof.

Description of the Prior Art:

10 [0002] In the performance of blood dialysis, the patient's blood is purified in the artificial kidney. Inside the artificial kidney, the purification of the blood is effected by keeping the dialytic solution circulated in the artificial kidney, allowing the dialytic solution to contact the blood through the medium of a permeable membrane, and causing the waste matter and water accompanied by the blood to pass into the dialytic solution. The dialytic solution is closely and impartially related to the improvement of the artificial kidney in performance. The acetate dialytic solution, the leader of the conventional dialytic solutions, is such that owing to the advance of the artificial kidney in quality, the acetic acid allowed to pass from this dialytic solution into the patient's vital organs has gained in quantity and the acetic acid causes the patient to suffer from such displeasing symptoms as headache and hypotension. Thus, it is giving place to the bicarbonate dialytic solution which exerts no appreciable burden upon the patient.

15 [0003] Unlike the acetate dialytic solution, the bicarbonate dialytic solution cannot be prepared as a single-component dope because sodium hydrogen carbonate present therein, on reaction with calcium or magnesium, gives rise to a precipitate. The bicarbonate dialytic solution, therefore, is prepared as a two-component composition comprising sodium hydrogen carbonate (principal solution) and a component containing calcium, magnesium, sodium, etc. (formulating liquid).

20 [0004] The principal component is prepared in the form of powder or solution and the formulating component in the form of solution. The amount of the principal component to be used is in the range of 500 to 1,000 g as powder or 10 to 12 liters as liquid and that of the formulating component in the range of 9 to 12 liters as liquid respectively per patient. In an institute abounding in patients, the work of transferring storage tanks of the dialytic solution exerts a heavy burden on workers. In an institute capable of performing dialysis simultaneously on 20 patients, for example, the doses of both 25 principal component and formulating component in a total amount enough for 40 patients (about 380 to 480 kg) must be transferred. The institute suffers also from the problem that the transfer and storage of these doses call for engagement of human labor and require preservation of floor spaces.

30 [0005] In the light of the true state of affairs described above, efforts are directed to decreasing the weight of the dialytic preparation by producing this preparation in the form of powder. JP-B-58-27,246 (1983), for example, discloses as means for uniform dispersion of a liquid acid a method for producing an electrolytic compound powder of the bicarbonate dialysis quality by powder mixing using a microfine powder of sodium chloride acidified with acetic acid. JP-A-62-30,540 (1987), concerning the production of a preparation for dialysis using sodium acetate as a principal component, discloses a technique for decreasing dispersion of the contents of such microconstituents as $MgCl_2 \cdot 6H_2O$ and $CaCl_2 \cdot 2H_2O$ in the dialytic solution obtained from a dialytic preparation having sodium acetate as a principal component 35 by intimately mixing these microconstituents with sodium acetate and water and converting the resultant mixture into fine powder. EP-A-0 177 614 discloses a preparation for blood dialysis comprising a first powdery composition comprising solid electrolytes and a liquid acid and a second powdery composition comprising sodium hydrogencarbonate.

40 [0006] In the powdery preparation for dialysis of the type using sodium hydrogen carbonate as a principal component, calcium chloride and magnesium chloride exhibit a deliquescent property and sodium chloride possibly acquires enhanced hygroscopicity in the presence of calcium chloride and magnesium chloride. This preparation, therefore, undergoes deliquescence or solidification during the course of production, transfer, or storage and entails the disadvantage that it betrays notable dispersion of composition and inferior stability during protracted preservation. Further, since this preparation uses acetic acid as a liquid acid, it possesses a high vapor pressure and readily succumbs to volatilization even when it is adsorbed on an inorganic salt, and lacks stability and workability. In recent years, the practice 45 of curbing possible variation in the blood sugar level by adding glucose to the dialytic solution has been finding acceptance in the field of clinical medicine. None of the preparations heretofore produced for dialysis has proved to be capable of retaining stability in protracted preservation.

50 [0007] An object of this invention, therefore, is to provide a novel preparation for dialysis and a method for the production thereof.

55 [0008] Another object of this invention is to provide a preparation for dialysis, which excels in the ability to withstand the impact of transfer and storage and in the maintenance of uniformity and stability of powder production.

SUMMARY OF THE INVENTION

[0009] The objects are accomplished by a preparation for blood dialysis comprising two compositions, i.e. a first powdery composition comprising solid electrolytes for dialysis, glucose, and acetic acid and a second powdery composition comprising sodium hydrogen carbonate, wherein the acetic acid is specifically adsorbed on granules of the solid sodium acetate-containing electrolytes for dialysis. The present invention further discloses a preparation for blood dialysis, wherein the preparation, on being dissolved in a prescribed amount of water, produces the following components of solid electrolytes for dialysis, glucose, and acetic acid from the first composition:

10	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="padding: 2px;">Na^+</td><td style="padding: 2px;">90 to 140 mmols</td></tr> <tr> <td style="padding: 2px;">K^+</td><td style="padding: 2px;">0 to 4 mmols</td></tr> <tr> <td style="padding: 2px;">Ca^{++}</td><td style="padding: 2px;">0.5 to 2.2 mmols</td></tr> <tr> <td style="padding: 2px;">Mg^{++}</td><td style="padding: 2px;">0.2 to 1.0 mmol</td></tr> <tr> <td style="padding: 2px;">Cl^-</td><td style="padding: 2px;">90 to 140 mmols</td></tr> <tr> <td style="padding: 2px;">CH_3COO^-</td><td style="padding: 2px;">6 to 15 mmols</td></tr> <tr> <td style="padding: 2px;">Glucose</td><td style="padding: 2px;">4 to 12 mmols</td></tr> </table>	Na^+	90 to 140 mmols	K^+	0 to 4 mmols	Ca^{++}	0.5 to 2.2 mmols	Mg^{++}	0.2 to 1.0 mmol	Cl^-	90 to 140 mmols	CH_3COO^-	6 to 15 mmols	Glucose	4 to 12 mmols
Na^+	90 to 140 mmols														
K^+	0 to 4 mmols														
Ca^{++}	0.5 to 2.2 mmols														
Mg^{++}	0.2 to 1.0 mmol														
Cl^-	90 to 140 mmols														
CH_3COO^-	6 to 15 mmols														
Glucose	4 to 12 mmols														
15															

and the following components of sodium hydrogen carbonate from the second composition:

20	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="padding: 2px;">Na^+</td><td style="padding: 2px;">15 to 40 mmols</td></tr> <tr> <td style="padding: 2px;">HCO_3^-</td><td style="padding: 2px;">15 to 40 mmols</td></tr> </table>	Na^+	15 to 40 mmols	HCO_3^-	15 to 40 mmols
Na^+	15 to 40 mmols				
HCO_3^-	15 to 40 mmols				

25 The present invention further discloses a preparation for blood dialysis, wherein the first solid composition for dialysis and a desiccant (moisture absorbent) are contained in a moistureproof packing material having moisture permeability (20°C) of not more than $2.0 \text{ g/cm}^2 \cdot 24\text{hrs}$.

[0010] The objects described above are further accomplished by a method for the production of a preparation for blood dialysis comprising two compositions, i.e. a first powdery composition comprising solid electrolytes for dialysis, glucose, and acetic acid wherein acetic acid is specifically adsorbed on granules of said solid electrolytes containing sodium acetate, and a second powdery composition comprising sodium hydrogen carbonate.

[0011] The method is characterized by the fact that the first composition is produced by mixing the components of the solid electrolytes for dialysis containing sodium acetate and glucose, pulverizing and granulating the resultant mixture, and subsequently mixing the resultant granules with the liquid acid.

[0012] These objects are further accomplished by a method for the production of a preparation for blood dialysis comprising two compositions, i.e. a first powdery composition comprising solid electrolytes for dialysis, glucose, and acetic acid wherein acetic acid is specifically adsorbed on granules of said solid electrolytes containing sodium acetate, and a second powdery composition comprising sodium hydrogen carbonate.

[0013] The method is characterized by the fact that the first composition is produced by spraying an aqueous solution of the components of the solid electrolytes for dialysis other than sodium chloride containing sodium acetate into a fluidized bed of a mixed powder of sodium chloride and glucose and, at the same time, granulating the wet mixed powder, and mixing the resultant granules with the liquid acid.

EXPLANATION OF THE PREFERRED EMBODIMENT

45 [0014] The preparation for blood dialysis according with the present invention comprises two compositions, i.e. a first powdery composition comprising solid electrolytes for dialysis, glucose, and acetic acid wherein acetic acid is specifically adsorbed on granules of said solid electrolytes containing sodium acetate and a second powdery composition comprising sodium hydrogen carbonate.

50 [0015] The solid electrolytes for dialysis which are usable for the first composition include sodium chloride, potassium chloride, calcium chloride, magnesium chloride, and sodium acetate, for example. Acetic acid is used as a pH-adjusting agent. This acetic acid is generally adsorbed specifically by the granules of the solid electrolyte for dialysis, particularly by the sodium acetate contained in the granules.

[0016] The first composition is preferable, on being dissolved in a prescribed amount of water, to produce the following components of solid electrolytes for dialysis and acetic acid:

55	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="padding: 2px;">Na^+</td><td style="padding: 2px;">90 to 140 mmols</td></tr> <tr> <td style="padding: 2px;">K^+</td><td style="padding: 2px;">0 to 4 mmols</td></tr> </table>	Na^+	90 to 140 mmols	K^+	0 to 4 mmols
Na^+	90 to 140 mmols				
K^+	0 to 4 mmols				

(continued)

Ca ⁺⁺	0.5 to 2.2 mmols
Mg ⁺⁺	0.2 to 1.0 mmol
Cl ⁻	90 to 140 mmols
CH ₃ COO ⁻	6 to 15 mmols
Glucose	4 to 12 mmols

5

10 preferably:

15

Na ⁺	100 to 130 mmols
K ⁺	1.5 to 3 mmols
Ca ⁺⁺	0.75 to 1.8 mmols
Mg ⁺⁺	0.3 to 0.8 mmol
Cl ⁻	100 to 130 mmols
CH ₃ COO ⁻	8 to 12 mmols
Glucose	6 to 10 mmols

20

[0017] The average particle size of the first composition is in the range of 10 to 200 mesh, preferably 14 to 100 mesh, of standard sieves.

[0018] The first composition is desired to be produced by either the dry method or the fluidized-bed method.

25

[0019] By the dry method, the first composition is obtained by stirring and mixing the solid electrolytes for dialysis containing sodium acetate and glucose with a stirring and mixing device such as a vertical granulator, for example, then pulverizing the mixed solid electrolytes with a pulverizing device such as a pin mill mixing the pulverized solid electrolytes with a stirring and mixing device such as a vertical granulator, for example, granulating the resultant mixture with a dry granulating device such as a roller compacter, for example, combining the resultant granules with the liquid acid, and mixing them with a stirring and mixing device such as a vertical granulator or a Nauter mixer, for example.

30

[0020] By the fluidized-bed method, the first composition is obtained by dissolving the solid electrolytes for dialysis other than sodium chloride containing sodium acetate in water of an amount 0.8 to 30 times, preferably 1.5 to 15 times, the amount of the solid electrolytes, spraying the resultant aqueous solution into a fluidized bed from of a mixed powder of sodium chloride and glucose powder inside a fluidized-bed granulating device and, at the same time, granulating the wet powder, combining the resultant granules with the liquid acid, and mixing them with a stirring and mixing device such as a vertical granulator or a Nauter mixer, for example. The mixed powder of sodium chloride and glucose is obtained, for example, by mixing them with a stirring and mixing device such as a vertical granulator or a Nauter mixer.

35

[0021] The second composition is a powder comprising sodium hydrogen carbonate. When this second composition is dissolved in a prescribed amount of water, the sodium hydrogen carbonate produces 15 to 40 mmols of Na⁺ and 15 to 40 mmols of HCO₃⁻, preferably 20 to 30 mmols of Na⁺ and 20 to 30 mmols of HCO₃⁻. The average particle size of the second composition is not more than 500 µm, preferably in the range of 200 to 10 µm.

40

[0022] The first and second compositions which are produced as described above are placed in separate containers. Prior to use, these compositions are dissolved in water and the resultant aqueous solution is supplied to the artificial kidney, there to be used as a liquid for blood dialysis.

45

[0023] The packing material to be used for containing these compositions is as already described. The first and second compositions are preferable to be each contained in a packing material in combination with an air-permeable container filled with a desiccator such as silica gel, a synthetic zeolite type moisture absorbent, or a calcium carbonate type moisture absorbent.

50

[0024] The packing material to be used for containing these compositions is preferable to possess low moisture permeability. It is preferable, for example, to use a moistureproof packing material possessing moisture permeability (20°C) of not more than 2.0 g/m² ·24hrs. As one packing material fulfilling this requirement, there may be cited a laminate film which is obtained by superposing polyethylene terephthalate/polyethylene/aluminum foil/polyethylene layers measuring 12 µm, 15 µm, 7 µm, and 30 µm respectively in thickness (moisture permeability 0.1 g/m² ·24hrs).

[0025] Now, the present invention will be described more specifically below with reference to working examples. Wherever the term "parts" is used in the working examples, it is meant as "parts by weight" unless otherwise specified.

55

Example 1

[0026] In a vertical granulator (stirring and mixing device produced by Fuji Sangyo K.K. and marketed under product

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code of "VG-25P"), 2188.7 parts of sodium chloride, 52.2 parts of potassium chloride, 77.2 parts of calcium chloride [$\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$], 35.6 parts of magnesium chloride [$\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$], 215.3 parts of sodium acetate [$\text{CH}_3\text{COONa} \cdot 3\text{H}_2\text{O}$], and 525 parts of glucose were mixed by stirring. Then, the resultant mixture was pulverized with a pin mill (pulverizing device produced by Fuji Sangyo K.K. and marketed under trademark designation of "Kollplex 16Z"), and further mixed
 5 by stirring with the vertical granulator. The resultant mixture was pelletized with a roller compacter (dry granulating device produced by Turbo Kogyo K.K. and marketed under product code of "WP-160X60"). The granules and 41.5 parts of acetic acid added thereto were mixed by stirring with the vertical granulator. The first composition consequently obtained was found to have a particle size distribution as follows.

	Mesh	%
10	-12	7.79
	12-32	51.41
15	32-48	6.70
	48-80	3.56
	80-150	2.75
	150-	27.82
	Average particle diameter	12-32 meshes

20 [0027] Separately, powdery sodium hydrogen carbonate was prepared as the second composition.

Example 2

25 [0028] An aqueous solution was obtained by dissolving 52.2 parts of potassium chloride, 77.2 parts of calcium chloride [$\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$], 35.6 parts of magnesium chloride [$\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$], 357.2 parts of sodium acetate [$\text{CH}_3\text{COONa} \cdot 3\text{H}_2\text{O}$] in water of an amount 5 times the amount of the inorganic salts. Separately, granules obtained by mixing by stirring 2188.7 parts of sodium chloride and 525 parts of glucose with the vertical granulator were fluidized within a fluidized-bed pelletizer (produced by Fuji Sangyo K.K. and marketed under product code of "STREA-15") and the fluidized bed of the granules was sprayed with the aforementioned aqueous solution to gain in weight. The granules
 30 thus obtained were placed in the vertical granulator and were then mixed by stirring with 41.5 parts of acetic acid added thereto. The first composition consequently obtained was found to have a particle size distribution as follows.

	Mesh	%
35	-12	1.20
	12-32	10.23
	32-48	17.21
40	48-80	40.32
	80-150	26.87
	150-	4.17
	Average particle diameter	40-80 meshes

[0029] Separately, powdery sodium hydrogen carbonate was prepared as the second composition.

45 Comparative Example

50 [0030] The first composition obtained in Example 2 was placed, as not accompanied with any desiccator, in a bag made of a laminate film obtained by superposing polyethylene terephthalate (12 μm), polyethylene (15 μm), aluminum foil (7 μm), and polyethylene (30 μm) layers and tested for stability in storage at 40°C. The results were as shown in Table 0.

Table 0

	Item	0 month	1 month	2 months
55	Color difference (ΔE)	0.00	9.77	14.99
	Residual ratio of acetic acid ion (%)	100.0	98.9	98.9
	Occurrence of aggregation	Yes	Yes	Yes

[0031] The "color difference (ΔE)" represents the numerical value (absolute number) determined by the use of a colorimetric system (produced by Minolta Camera K.K. and marketed under product code of "CD-200"). The "residual ratio of acetic acid ion" represents the magnitude determined by dissolving part of a sample in water and examining the resultant aqueous solution by high-speed liquid chromatography (by the use of a system produced by Nippon Bunko K. K. and marketed under product code of "BIP-I").

5

Example 3

[0032] The first composition obtained in Example 2 was placed in combination with silica gel as a desiccant in a bag made of a laminate film obtained by superposing polyethylene terephthalate (12 μm), polyethylene (15 μm), aluminum foil (7 μm), and polyethylene (30 μm) layers and tested for stability in storage at 40°C. The results were as shown in Table 1.

10

Table 1

Item	0 month	1 month	2 months
Color difference (ΔE)	0.00	0.52	0.92
Residual ratio of acetic acid ion (%)	100.0	98.9	98.9
Occurrence of aggregation	No	No	No

20

Example 4

[0033] The first composition obtained in Example 1, a composition produced by following the procedure of Example 1 except that the addition of sodium acetate was omitted (composition of Control 1), and a mixture of 2188.7 parts of sodium chloride and 41.5 g of acetic acid (composition of Control 2) were left standing in the open air at 30°C for 30 minutes and then tested for residual ratio of acetic acid. The results were as shown in Table 2.

25

Table 2

Time	Composition of		
	Example 1	Control 1	Control 2
Immediately after production	100%	100%	100%
After 30 minutes following production	100.2%	17.6%	12.7%

35

[0034] It is clearly noted from Table 2 that the preparations for blood dialysis according with the present invention show specific adsorption of acetic acid by sodium acetate and excel in stability in preservation.

30

Example 5

40

[0035] In a vertical granulator (stirring and mixing device produced by Fuji Sangyo K.K. and marketed under product code of "VG-25P"), 2188.7 parts of sodium chloride, 52.2 parts of potassium chloride, 77.2 parts of calcium chloride [$\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$], 35.6 parts of magnesium chloride [$\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$], 175.3 parts of sodium acetate, and 521.5 parts of glucose were mixed by stirring. Then, the resultant mixture was pulverized with a pin mill (pulverizing device produced by Fuji Sangyo K.K. and marketed under trademark designation of "Kollplex 16Z") and the resultant powder was mixed by stirring with the vertical granulator. The resultant mixture was pelletized with a roller compacter (dry granulating device produced by Turbo Kogyo K.K. and marketed under product code of "WP-160X60"). The granules and 41.5 parts of acetic acid added thereto were mixed by stirring with the vertical granulator. The first composition consequently obtained was found to have a particle size distribution as follows.

45

50

Mesh	%
-12	0.20
12-32	47.11
32-48	16.35
48-80	7.29
80-150	5.38
150-	23.17

55

Example 6

[0036] An aqueous solution was obtained by dissolving 52.2 parts of potassium chloride, 77.2 parts of calcium chloride [$\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$], 175.3 parts of sodium acetate, and 35.6 parts of magnesium chloride [$\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$] in 1500 parts of water (about 3 times the amount of the electrolytes). Separately, 2188.7 parts of sodium chloride and 525 parts of glucose were mixed by stirring with the vertical granulator. The resultant mixture was fluidized within a fluidized-bed pelletizer (produced by Fuji Sangyo K.K. and marketed under product code of "STREA-15"). The fluidized bed of the powder was sprayed with the aforementioned aqueous solution to gain in weight. The granules thus obtained were placed in the vertical granulator and mixed by stirring with 41.5 parts of acetic acid added thereto. The first composition consequently obtained was found to have a particle size distribution as follows.

Mesh	%
-12	0.82
12-32	8.78
32-48	15.57
48-80	44.14
80-150	25.74
150-	4.76

Example 7

[0037] The first composition obtained in Example 6 was placed, as not accompanied by any desiccator, in a bag made of a laminate film obtained by superposing polyethylene terephthalate (12 μm), polyethylene (15 μm), aluminum foil (7 μm), and polyethylene (30 μm) layers and tested for stability in storage at 40°C. The results were as shown in Table 3.

Table 3

Item	0 month	1 month	2 months
First composition			
Color difference (ΔE)	0.00	0.05	0.11
Residual ratio of acetic acid ion (%)	100.0	99.9	99.7
Occurrence of aggregation	No	No	No

[0038] The "color difference (ΔE)" represents the numerical value (absolute number) determined by the use of a colorimetric system (produced by Minolta Camera K.K. and marketed under product code of "CD-200"). The "residual ratio of acetic acid ion" represents the magnitude determined by dissolving part of a sample in water and examining the resultant aqueous solution by high-speed liquid chromatography (by the use of a system produced by Nippon Bunko K.K. and marketed under product code of "BIP-I").

Example 8

[0039] In a vertical granulator (stirring and mixing device produced by Fuji Sangyo K.K. and marketed under product code of "VG-25P"), 1038.6 parts of sodium chloride, 52.2 parts of potassium chloride, 77.2 parts of calcium chloride [$\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$], 35.6 parts of magnesium chloride [$\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$], 175.3 parts of sodium acetate [$\text{CH}_3\text{COONa} \cdot 3\text{H}_2\text{O}$], and 525 parts of glucose were mixed by stirring. The resultant mixture was then pulverized with a pin mill (pulverizing device produced by Fuji Sangyo K.K. and marketed under trademark designation of "Kollplex 16Z"). The resultant powder was further mixed by stirring with the vertical granulator. The mixture consequently obtained was pelletized with a roller compacter (dry granulating device produced by Turbo Kogyo K.K. and marketed under product code of "WP-160X60"). The granules and 41.5 parts of acetic acid added thereto were mixed by stirring with the vertical granulator. The first composition obtained as the result was found to have a particle size distribution as follows.

Mesh	%
-12	3.25
12-32	24.38

(continued)

Mesh	%
32-48	26.71
48-80	9.21
80-150	5.51
150-	30.94

10 Example 9

15 [0040] An aqueous solution was obtained by dissolving 52.2 parts of potassium chloride, 77.2 parts of calcium chloride [$\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$], and 290.8 parts of sodium acetate [$\text{CH}_3\text{COONa} \cdot 3\text{H}_2\text{O}$] in 1500 parts of water. Separately, 1038.6 parts of sodium chloride and 525 parts of glucose were mixed by stirring with the vertical granulator. The resultant mixture was fluidized within a fluidized-bed pelletizer (produced by Fuji Sangyo K.K. and marketed under product code of "STREA-15"). The fluidized bed of the powder was sprayed with the aforementioned aqueous solution to gain in weight. The granules obtained as described above were placed in the vertical granulator and were mixed by stirring with 41.5 parts of acetic acid added thereto. The first composition consequently obtained was found to have a particle size distribution as follows.

20

Mesh	%
-12	2.37
12-32	9.36
32-48	16.81
48-80	43.44
80-150	23.98
150-	4.04

25

30 Control 3

35 [0041] A first composition obtained by following the procedure of Example 6 except that the addition of sodium acetate was omitted was placed in the same packing material as used in Example 7 and tested for stability in storage at 40°C. The results were as shown in Table 4.

[0042] It is clearly noted from Table 4 that the compositions according with the present invention excelled those of Control 3 in terms of coloration, aggregation, and residual ratio of acetic acid ion.

Table 4

Item	0 month	1 month	2 months
First composition			
Color difference (ΔE)	0.00	0.69	2.07
Residual ratio of acetic acid ion (%)	100.0	87.6	76.5
Occurrence of aggregation	Yes	Yes	Yes

45

50 [0043] The "color difference (ΔE)" represents the numerical value (absolute number) determined by the use of a colorimetric system (produced by Minolta Camera K.K. and marketed under product code of "CD-200"). The "residual ratio of acetic acid ion" represents the magnitude determined by dissolving part of a sample in water and examining the resultant aqueous solution by high-speed liquid chromatography (by the use of a system produced by Nippon Bunko K.K. and marketed under product code of "BIP-I").

55 [0044] The preparation for blood dialysis according with the present invention is extremely light as compared with the conventional dialytic solution because it comprises two compositions, i.e. a first powdery composition comprising solid electrolytes for dialysis, glucose, and acetic acid wherein acetic acid is specifically adsorbed by granules of said solid electrolytes containing sodium acetate and a second powdery composition comprising sodium hydrogen carbonate. Acetic acid is used as a pH-adjusting agent, and the preparation enjoys the advantage that it exhibits highly satisfactory stability in protracted preservation because the acetic acid is specifically adsorbed by the sodium acetate in the solid electrolytes.

[0045] Further, since the preparation for blood dialysis contained in combination with a desiccant in a moistureproof packing material, it has the advantage that it is retained very stably in the state of low moisture.

5 [0046] The preparation for blood dialysis according with the present invention is produced by the dry method or the fluidized-bed method. In spite of the use of calcium chloride or magnesium chloride, a substance which has heretofore defined uniform pulverization because of an excessively high deliquescent property, the powdery compositions of the preparation can be homogenized. Further, the problem that the components of the compositions cannot be easily distributed uniformly can be precluded by the aforementioned method of production.

10 **Claims**

1. A preparation for blood dialysis comprising two compositions, i.e. a first powdery composition comprising solid electrolytes for dialysis, glucose and acetic acid, wherein said acetic acid is specifically adsorbed by granules of said solid electrolytes containing sodium acetate, and a second powdery composition comprising sodium hydrogen carbonate.
- 15 2. The preparation of claim 1, which on being dissolved in a prescribed amount of water produces the following components of solid electrolytes for dialysis, glucose, and acetic acid from said first composition :

20

Na ⁺	90 à 140 mmols
K ⁺	0 to 4 mmols
Ca ⁺⁺	0.5 to 2.2 mmols
Mg ⁺⁺	0.2 to 1.0 mmol
Cl ⁻	90 to 140 mmols
CH ₃ COO ⁻	6 to 15 mmols
Glucose	4 to 12 mmols

25

and the following components of said sodium hydrogen carbonate from said second composition :

30

Na ⁺	15 to 40 mmols
HCO ₃ ⁻	15 to 40 mmols

- 35 3. The preparation of claim 1 or 2, wherein said first composition is contained, together with a dessicant, in a moistureproof packing material having a moisture permeability (20°C) of not more than 2.0 g/cm²•24 hrs.
4. A method for the production of a preparation for blood dialysis as defined in claim 1, which method comprises preparing said first composition by mixing the components of said solid electrolytes for dialysis containing sodium acetate and glucose, pulverizing and then granulating the resultant mixture, and then mixing the resultant granules with acetic acid.
- 40 5. A method for the production of a preparation for blood dialysis as defined in claim 1, which method comprises preparing said first composition by spraying an aqueous solution of the components of said solid electrolytes for dialysis other than sodium chloride and containing sodium acetate into a fluidized bed of a mixed powder of sodium chloride and glucose and, at the same time, granulating the wet mixed powder, and mixing the resultant granules with acetic acid.

50 **Patentansprüche**

1. Präparat für die Blutdialyse, umfassend zwei Zusammensetzungen, d.h. eine erste pulvelförmige Zusammensetzung, die Festelektrolyte für die Dialyse, Glucose und Essigsäure umfaßt, wobei die Essigsäure durch Körner der Feststoffelektrolyten, die Natriumacetat enthalten, spezifisch adsorbiert wird, sowie eine zweite pulvelförmige Zusammensetzung, die Natriumhydrogencarbonat umfaßt.
- 55 2. Präparat nach Anspruch 1, welches bei Lösung in einer vorbestimmten Menge Wasser die folgenden Komponenten an Festelektrolyten für die Dialyse, Glucose und Essigsäure aus der ersten Zusammensetzung:

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Na ⁺	90 bis 140 mmol
K ⁺	0 bis 4 mmol
Ca ²⁺	0,5 bis 2,2 mmol
Mg ²⁺	0,2 bis 1,0 mmol
Cl ⁻	90 bis 140 mmol
CH ₃ COO ⁻	6 bis 15 mmol
Glucose	4 bis 12 mmol

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sowie die folgenden Komponenten des Natriumhydrogencarbonats aus der zweiten Zusammensetzung erzeugt:

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Na ⁺	15 bis 40 mmol
HCO ₃ ⁻	15 bis 40 mmol

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- 3. Präparat nach Anspruch 1 oder 2, wobei die erste Zusammensetzung zusammen mit einem Trockenmittel in einem feuchtigkeitsbeständigen Verpackungsmaterial mit einer Feuchtigkeitsdurchlässigkeit (20°C) von nicht mehr als 2,0 g/cm² · 24 h enthalten ist.
- 20 4. Verfahren zur Herstellung eines Präparats zur Blutdialyse gemäß Anspruch 1, umfassend die Herstellung der ersten Zusammensetzung durch Vermischen der Komponenten der Festelektrolyte für die Dialyse, die Natriumacetat enthalten, und Glucose, Pulverisieren und anschließendes Granulieren des erhaltenen Gemisches, sowie durch anschließendes Vermischen der erhaltenen Körner mit Essigsäure.
- 25 5. Verfahren zur Herstellung eines Präparats zur Blutdialyse gemäß Anspruch 1, umfassend die Herstellung der ersten Zusammensetzung durch Sprühen einer wässrigen Lösung der von Natriumchlorid verschiedenen, Natriumacetat enthaltenden Komponenten der Festelektrolyte für die Dialyse in ein Fließbett des Pulvergemisches aus Natriumchlorid und Glucose und gleichzeitiges Granulieren des nassen Pulvergemisches und Vermischen der erhaltenen Körner mit Essigsäure.

Revendications

- 35 1. Préparation pour la dialyse du sang comprenant deux compositions, à savoir une première composition pulvérulente comprenant des électrolytes solides pour la dialyse, du glucose et de l'acide acétique, où l'acide acétique est spécifiquement adsorbé par des granulés desdits électrolytes solides contenant de l'acétate de sodium, et une seconde composition pulvérulente comprenant de l'hydrogénocarbonate de sodium.
- 40 2. Préparation selon la revendication 1 qui, lorsqu'elle est dissoute dans une quantité d'eau prescrite, produit les composants suivants d'électrolytes solides pour la dialyse, de glucose et d'acide acétique à partir de ladite première composition :

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Na ⁺	90 à 140 mmoles
K ⁺	0 à 4 mmoles
Ca ²⁺	0,5 à 2,2 mmoles
Mg ²⁺	0,2 à 1,0 mmoles
Cl ⁻	90 à 140 mmoles
CH ₃ COO ⁻	6 à 15 mmoles
Glucose	4 à 12 mmoles

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et les composants suivants d'hydrogénocarbonate de sodium à partir de ladite seconde composition :

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Na ⁺	15 à 40 mmoles
HCO ₃ ⁻	15 à 40 mmoles.

- 3. Préparation selon la revendication 1 ou 2, dans laquelle ladite première composition est contenue, en même temps

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qu'un desséchant, dans un matériau d'emballage étanche à l'humidité ayant une perméabilité à l'humidité (20°C) qui ne dépasse pas 2,0 g/cm²-24 h.

- 5 4. Procédé pour la production d'une préparation pour la dialyse du sang telle que définie dans la revendication 1, lequel procédé comprend la préparation de ladite première composition par mélange des composants desdits électrolytes solides pour la dialyse contenant de l'acétate de sodium et du glucose, pulvérisation puis granulation du mélange résultant, puis mélange des granulés résultants avec de l'acide acétique.
- 10 5. Procédé pour la production d'une préparation pour la dialyse du sang telle que définie dans la revendication 1, lequel procédé comprend la préparation de ladite première composition par pulvérisation d'une solution aqueuse des composants desdits électrolytes solides pour la dialyse, contenant de l'acétate de sodium, autres que le chlorure de sodium dans un lit fluidisé d'une poudre mixte de chlorure de sodium et de glucose et, en même temps, granulation de la poudre mixte humide, et mélange des granulés résultants avec de l'acide acétique.

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